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When visual perception causes feeling: Enhanced cross-modal processing in grapheme-color synesthesia

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In synesthesia, stimulation of one sensory modality (e.g., hearing) triggers a percept in another, non-stimulated sensory modality (e.g., vision). Likewise, perception of a form (e.g., a letter) may induce a color percept (i.e., grapheme-color synesthesia). To date, the neural mechanisms underlying synesthesia remain to be elucidated. We disclosed by fMRI, while controlling for surface color processing, enhanced activity in the left intraparietal cortex during the experience of grapheme-color synesthesia (n = 9). In contrast, the perception of surface color per se activated the color centers in the fusiform gyrus bilaterally. The data support theoretical accounts that grapheme-color synesthesia may originate from enhanced cross-modal binding of form and color. A mismatch of surface color and grapheme induced synesthetically felt color additionally activated the left dorsolateral prefrontal cortex (DLPFC). This suggests that cognitive control processes become active to resolve the perceptual conflict resulting from synesthesia.

Introduction

In synesthetes stimulation of one sensory modality automatically triggers an additional percept in another, primarily non-stimulated modality. The most common form of synesthesia is 'colored hearing' (auditory–visual synesthesia), which encompasses both music-color and word-color synesthesia (Baron-Cohen and Harrison, 1997). Word-color synesthesia is further subdivided into the following: grapheme-color synesthesia, in which the prominent letter within a word induces a specific color experience; phoneme-color synesthesia, in which the color experience is determined by the phonemes; and the rare lexical-color synesthesia (Weiss et al., 2001), in which a particular word triggers a specific color response.

Synesthesia, in its original sense, involves 'abnormal' perceptions across sensory modalities. However, much can be learned about synesthesia, especially grapheme-color synesthesia, by examining synesthetic experiences within the same sensory modality, i.e., vision. Accordingly, many psychophysical studies of grapheme-color synesthesia (Dixon et al., 2000; Mattingley et al., 2001; Ramachandran and Hubbard, 2001) made use of the fact that grapheme-color synesthetes not only experience additional color percepts when hearing a letter (across modality), but also when seeing/reading it (within modality). For example, in grapheme-color synesthesia the synesthetic experience, i.e., the perception of a color, can be elicited both by a stimulus in another modality (hearing the letter/word) or by a stimulus of the same modality (seeing/reading the letter/word). When discussing this issue one should keep in mind, that even if the stimulus is heard rather than seen, grapheme-color synesthetes must access the visual form of the heard letters (or words containing the triggering letters, respectively) prior to their synesthetic (color) experience, since they experience similar colors for non-homophonemic words starting with the same letter (e.g., 'apple' vs. 'art'; see Paulesu et al., 1995). Therefore, in grapheme-color synesthesia the essential aspect of the stimulus letter or word seems to be their visual form (i.e., the graphemes) independent of how this visual form is accessed.

Despite a growing interest in synesthesia over the last years, to date the physiological basis of synesthesia remains elusive (Ramachandran and Hubbard, 2001). One influential theory hypothesizes enhanced cross-modal processing in synesthetes (Baron-Cohen et al., 1993; Baron-Cohen and Harrison, 1997). Consequently, functional imaging studies on color-word synesthesia tried to reveal activity within the visual (color) system, when synesthetes hear words. In the first functional imaging study on synesthesia (Paulesu et al., 1995), the comparison between words and tones revealed activation of language areas in both (grapheme-color) synesthetes (n = 6) and non-synesthetes. In synesthetes, however, additional activations of visual associative areas, espe-

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cially in the inferior temporal cortex, but no activation of areas V1, V2 or V4 were found. In contrast, subsequent studies of synesthesia showed activation of V1, but not V4 (1 grapheme-color synesthete; Aleman et al., 2001), or activated (left) V4, but not V1 (word-color synesthetes, $n = 13$; Nunn et al., 2002). Besides yielding such conflicting results about activation of "lower" tier visual areas, these studies did not reveal where the hypothesized cross-modal transfer (Baron-Cohen et al., 1993) might take place, i.e., the 'binding' of internal synesthetic color experience and, e.g., external visual (alphanumeric) form. A recent psychophysical study using binocular or motion cues to create synesthesia-inducing alphanumeric forms implies 'a central locus of visual processing for synesthetic binding of form and color' (Palmeri et al., 2002). Consistent with this hypothesis, Mattingley et al. (2001) state 'that automatic binding of color and alphanumeric form in synesthesia arises after initial processes of letter and digit recognition are complete'. Evidence for the latter claim is provided by a psychophysical study where grapheme-color synesthesia was eliminated when the synesthesia inducing alphanumeric forms were masked after presentation, so that the forms were processed, as indicated by interference effects, but were nevertheless unavailable for conscious report (Mattingley et al., 2001).

The latter observation speaks against a crucial node for the binding of alphanumeric form and synesthetic color within "lower" tier visual system. Rather, synesthesia may result from processes in cross-modal brain areas, where information from different sensory modalities may converge. Candidate regions for binding form and color are the (posterior) inferior temporal (PIT) cortex and the intraparietal sulcus (IPS). In both macaque and man, PIT neurons have access to and seem to integrate color and shape information (Corbetta et al., 1991) (see also the discussion of the word form area; Price and Devlin, 2003). Likewise, recent functional imaging studies of the human IPS revealed that it contains (as in the macaque) a mosaic of polymodal areas (Bremmer et al., 2001; Grefkes et al., 2002, 2004; Sereno et al., 2001; Shikata et al., 2003). Of these areas anterior intraparietal area (AIP) (Grefkes et al., 2002) and caudal intraparietal area (CIP) (Shikata et al., 2003), where visual form information is combined with input from other sensory modalities or with other visual information, could play a role in grapheme-color synesthesia.

Accordingly, this fMRI study was designed to reveal the neural mechanisms underlying grapheme-color synesthesia. In particular, we were interested to depict where in the human brain the hypothesized binding of alphanumeric form and synesthetic color occurs: 9 grapheme-color synesthetes were visually presented with individually selected alphanumeric forms (letters), which either induced a specific, individual synesthetic color experience or not. The presence or absence of synesthesia was reported by button presses. In contrast to previous functional imaging studies of synesthesia, in which synesthetes passively listened to words (Nunn et al., 2002; Paulesu et al., 1995), this procedure ensured a behavioral control during scanning but avoided the problem of movement artefacts caused by overt speech in fMRI. To separate the neural mechanisms of color processing per se from the effects of synesthesia and to assess putative interactions thereof, in half of the trials the letter stimuli were presented in color, and in the other half of the trials in gray. This renders a two factorial design with the factors SYNESTHESIA (present [S+] vs. absent [S−]) and COLOR (colored [C+] vs. non-colored [C−] stimuli). Since we ensured for each individual that the surface color of a stimulus letter never matched the synesthetic color, the neural correlates of this perceptual mismatch can be examined by analysis of the interaction term. Again, there are two candidate regions which might be activated by this perceptual conflict and the cognitive control it requires: the dorsolateral prefrontal cortex (DLPFC) or the anterior cingulate cortex (ACC) (Fink et al., 1999; Koechlin et al., 2003; MacDonald et al., 2000; Stephan et al., 2003).

When interpreting the data one should keep in mind, however, that this factorial design is not fully balanced since the mismatch (and therefore any accompanying cognitive and neural processes) is a feature of the presentation of synesthesia-inducing colored letters and is absent in all other conditions. The interaction term therefore identifies a complex interaction: that of color, synesthetic experience and mismatch. Though this limits the interpretation of the interaction term this caveat would only be applicable to the interpretation of the main effect of synesthesia (i.e., our primary interest), if any regions implicated by the main effect were also identified by the interaction term.

Methods

Subjects and neuropsychological testing

Nine individuals with (grapheme-color) synesthesia (6 females, 3 males; mean age = 23.4 years; range 19–31 years) participated in the study. All synesthetes gave informed consent and the study was approved by the local ethics committee. Eight synesthetes were strongly right-handed, one female was ambidextrous (Oldfield, 1971). All participants were physically examined to exclude neurological impairments or problems of color vision (using the full version of the Ishihara plates; Ishihara, 1994). In addition, a neuropsychological test battery was employed, in which all subjects performed superior on tests of general intelligence (mean IQ = 120 ± 17) (Lehrl et al., 1995) and visuospatial abilities (Hooper Visual Organization Test, Fragmented Pictures Test, Visual Object and Space Perception test battery, Benton Line Orientation Test) (Lezak, 1995). Furthermore, subjects reported the features of their synesthesia using a questionnaire devised by Baron-Cohen et al. (1993). Consistent with previous reports in the literature, their synesthesia was present since childhood and some synesthetes reported that the condition ran in their families (Baron-Cohen and Harrison, 1997). As in previous studies, a test of consistency (Baron-Cohen et al., 1993) was used to verify the presence of genuine synesthesia. All participants were given a 116-item list containing the 26 letters of the alphabet (plus the three German 'Umlaute' ä, ö and ü), the digits 0–9 and the days of the week as well as 10 items of each of the following categories: objects, cities, male and female names, animals, professions and abstract nouns. For each of these 116 items, the specific synesthetic color experience of each synesthete was documented. Without warning, the list was again given to the synesthetes after at least 2 months (mean 3.5, range 2–8). The color responses of all synesthetes were highly consistent over time (rate of consistent responses: 96.4 ± 3.6%).

Stimuli and experimental design

According to their performance in the consistency test, individual sets of letter stimuli were created for each subject: in a particular synesthete, some letters of the alphabet induced

strong grapheme-color synesthesia (S+), while other letters did not (S−; see also Table 6, page 193, in Ortmann, 1933). During the fMRI experiment, these letter stimuli were visually presented either in color (C+), which was chosen so that the physical color of a stimulus letter never matched the synesthetic color induced by this very stimulus letter, or in light gray (C−). Light gray was chosen since during the neuropsychological testing our grapheme-color synesthetes reported this 'color' as the one appearing most neutral to them. This renders a 2 × 2 factorial design with four experimental conditions, which were presented in a block-wise manner: colored letters inducing synesthesia (C + S+), non-colored letters inducing synesthesia (C − S+), colored letters not inducing synesthesia (C + S−) and non-colored letters not inducing synesthesia (C − S−). This design allowed us to examine the physiological basis of color processing (main effect of COLOR: [C + S+ and C + S−] > [C − S+ and C − S−]) and synesthetic experience (main effect of SYNESTHESIA: [C + S+ and C − S+] > [C + S− and C − S−]) in grapheme-color synesthesia. Furthermore, the interaction of the neural mechanisms underlying processing simultaneously a physically evoked and a synesthetic color experience could be examined by assessing the interaction terms ([C + S+ > C − S+] > C + S− > C − S−] and [C + S− > C − S−] > [C + S+ > C − S+]). As already noted, this design is not fully balanced since the mismatch of surface and synesthetic color (and therefore any accompanying neural process) occurs only in the condition C + S+ and is absent in all other conditions. The interaction terms therefore identify a complex interaction: that of color, synesthetic experience and mismatch, which limits the interpretation of the interaction terms. However, this caveat would only apply to the main effect of SYNESTHESIA (i.e., our primary interest), if any regions implicated by the main effect were also identified by the interaction terms.

Experimental set-up and task

For visual presentation of the stimulus letters during the fMRI experiment, a mirror construction was used to reflect the stimulus display centrally into the visual field of the synesthetes. Stimulus letters were presented in light gray or in color on a black background. Lying in the MR scanner, synesthetes viewed the display from a distance of 26 cm (14 cm screen to mirror, 12 cm mirror to subject's eyes). Presentation and timing of stimuli was accomplished using MEL 4.0 (MEL Professional, Psychology Software Tools, Inc., Pittsburgh, USA). In each experimental block, 12 stimulus letters were shown. Each trial consisted of stimulus letter on time (SOT) of 1880 ms and an inter-stimulus interval (ISI) of 200 ms. Thus, each block of trials had a duration of 25 s. The experimental conditions (C + S+, C − S+, C + S−, C − S−) were separated from each other by baselines (each lasting 25 s), during which the instructions, which were identical for all conditions, were displayed. Subjects were explicitly required to read the instructions for the next block of trials repeatedly to ensure that the same cognitive task was performed in all baseline conditions. Apart from silently reading the instructions, no other task was performed during baselines. The baselines also prevented an overlap of neural activity between conditions by separating the cerebral hemodynamic responses specific to the different experimental conditions.

The instruction was as follows: "Please indicate by button press for each letter whether you experience synesthesia or not!" Therefore, as a within-experiment behavioral control synesthetes indicated via button presses of a tapping apparatus on the right of their body, whether or not the visually displayed letter induced a synesthetic color experience. If subjects experienced synesthesia they were asked to press a button with their right index finger. If subjects did not experience synesthesia they were asked to press another button with their right middle finger. They were asked to respond as quickly as possible. Subjects' responses and reaction times were recorded by an MR compatible tapping apparatus in which the button presses interrupted an optic fiber light beam. Prior to scanning, subjects were familiarized with the experimental set-up and the task.

Analysis of the responses and reaction times during scanning was performed using an ANOVA (with the within-subject factors SYNESTHESIA and COLOR). Subjects performance during fMRI scanning was consistent with their performance in the testing prior to scanning: One subject reported the experience of synesthesia for his individually selected stimulus letters in 94% of the trials, all other subjects experienced synesthesia in 100% of trials, when presented with their specific stimulus set during the C + S+ and C − S+ conditions. On the other hand, two subjects reported in 7.4% and 8.8% of the trials the experience of synesthesia during the C + S− and C − S− conditions. In all other subjects, the individual non-synesthesia-inducing stimulus sets did not trigger any synesthetic experience. The fact that the behavior of three subjects during scanning slightly differed from the expected performance would – if at all – reduce the statistical power of our analyses, i.e., make it harder to detect significant changes of neural activity associated with the respective contrasts. That the observed neural activations survive even stringent statistical thresholds speaks for the robustness of our findings.

Per baseline, five (whole brain) volumes (TR = 5 s) were acquired. Per block of trials of each experimental condition, also five (whole brain) volumes (TR = 5 s) were acquired. A total of three experimental runs each consisting of 12 baselines and 12 experimental conditions were performed, leading to the acquisition of a total of 360 volumes per subject (120 volume images per run). This scanning paradigm resulted in three repeats per condition per experimental run, leading to 9 repeats per condition per subject. The order of the experimental conditions was counterbalanced across runs and individuals.

MR hardware and technical parameters

Scanning was performed using a 1.5-T whole-body scanner (Siemens Vision, Erlangen, Germany) with echo-planar imaging (EPI) capability. For transmit and receive a standard radio-frequency head coil was used. Prior to functional neuroimaging high-resolution anatomical images were acquired using a T_1-weighted 3D MP-RAGE (magnetization-prepared, rapid acquisition gradient-echo) pulse sequence with the following parameters: TE = 4.4 ms, TR = 11.4 ms, TI (inversion time) = 300 ms, flip angle = 15°, slice thickness = 1.25 mm, FOV = 230 mm, matrix = 200 × 256, 128 sagittal slices. Functional MR images were acquired in axial plane with a gradient-echo EPI pulse sequence using blood-oxygen-level-dependent (BOLD) contrast. Sequence parameters were as follows: TE = 66 ms, TR = 5 s, flip angle = 90°, slice thickness = 3 mm, inter-slice-gap = 0.3 mm, FOV = 200 mm, in plane resolution = 3.125 mm × 3.125 mm, matrix = 64 × 64, 32 transversal slices. These 32 slices covered a subject's brain from the cerebellar vermis up to the vertex and

were oriented along the anterior–posterior commissure (AC–PC) line using a midsagittal scout image. The fMRI paradigm consisted of the 3 time series as described above. Each of these time series was preceded by 5 dummy images to allow the MR signal to reach steady state.

Image processing

Image processing and all statistical calculations were performed on Ultra 20 workstations (SUN Microsystems Computers, Palo Alto, CA, USA) using MATLAB (The Mathworks Inc., Natick, MA, USA) and SPM99 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). SPM99 was employed for image pre-processing (image realignment, co-registration, normalization and smoothing) and to create statistical maps of changes in relative regional BOLD responses corresponding to the four experimental conditions and the baseline (Friston et al., 1995a,c).

The first five images preceding each time series were discarded to allow the MR signal to reach steady state (see above). To correct for head movement between scans the remaining 120 volume images of each time series were realigned to the first image—that is, to the sixth image of each time series. Following realignment, all image sets were co-registered to the 3D anatomical images acquired prior to functional neuroimaging. For image co-registration, SPM99 and MPItool (Max-Planck Institute for Neurological Research, Cologne, Germany) were used. Thereafter, images were transformed using linear proportions and a non-linear sampling algorithm into standard stereotactic space with the inter-commissural AC–PC line being used as the reference plane (Friston et al., 1995a). The resulting voxel size was $2 \times 2 \times 2$ mm^3. For the normalization procedure a representative brain from the Montreal Neurological Institute (MNI) series provided by SPM99 was employed as the reference template (Evans et al., 1994). Subsequently, all data were expressed in standard stereotactic x-, y- and z-coordinates of the Talairach and Tournoux space convention (Talairach and Tournoux, 1988) using two non-linear transformations (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). Following normalization procedures, transformed data were smoothed with a Gaussian kernel of 10 mm (full-width half maximum) for the group analysis to compensate for normal variation in individual brain size and shape, as well as gyral and sulcal anatomy across subjects, and to meet the statistical requirements of the theory of Gaussian random fields presupposed by the general linear model employed in SPM99. To restrict analysis to intracranial regions, only voxels with values greater than 0.8 of the volume mean in all images were selected.

Statistical analyses

Following image pre-processing, statistical analyses of functional MR data were performed. Subject-specific low-frequency drifts in signal were modeled and removed using low-frequency cosine waves, and proportional scaling normalized the global means. Data analysis was performed by modeling the four experimental conditions (C + S+, C − S+, C + S−, C − S−) and the baseline by means of reference waveforms which correspond to boxcar functions convolved with a hemodynamic response function (Friston et al., 1995b,c). Accordingly, a design matrix which comprised contrasts modeling alternating intervals of "activation" (referring to the four different experimental conditions) and "baseline" was defined. Specific effects were assessed by applying appropriate linear contrasts to the parameter estimates of the four experimental conditions and the baselines resulting in t statistics for each voxel. These t statistics were then transformed to Z statistics constituting statistical parametric maps ($SPM_{\{Z\}}$) of differences between both the experimental conditions and between the experimental conditions and the baseline. $SPM_{\{Z\}}$ statistics were interpreted in light of the theory of probabilistic behavior of Gaussian random fields (Friston et al., 1995c).

Since (grapheme-color) synesthetes do not represent the general population and due to the small number of synesthetes available (n = 9), a fixed effect approach was initially used for the statistical analyses. For the fixed effect analysis, voxels had to pass a height threshold of $T = 4.52$ (corresponding to $Z = 4.6$; $P_c < 0.05$, corrected for multiple comparisons) in order to be identified as reflecting statistically significant activation; no extent threshold was applied.

In addition, small volume corrections were employed to allow for a (hypothesis-driven) region-of-interest (ROI)-based approach (Friston, 1997) to detect whether or not the color areas within the fusiform gyrus were activated during synesthesia. This ROI approach was used to increase our sensitivity, since in contrast to previous functional imaging studies focusing on color processing, which used full-screen multi-colored Mondrians as stimuli, our stimuli only consisted of single colored letters displayed on a black screen. A priori, x-, y- and z-coordinates (in Talairach and Tournoux space) for the putative positions of the color area (V4 proper) within the fusiform gyrus bilaterally were derived from a previous functional imaging study on cortical color processing using fMRI (McKeefry and Zeki, 1997) and were used to center the ROI for the current analysis: $x = +30$, $y = -75$ and $z = -19$ (right fusiform gyrus) and $x = -29$, $y = -68$ and $z = -14$ (left fusiform gyrus). The extent of the spherical ROI was set to 20 mm, that is, two times the Gaussian kernel used for smoothing the group data (see above). Therefore, the ROI most likely comprised the whole V4 complex (Zeki et al., 1991) including V4 proper, V4α, V4v (Sereno et al., 1995) and V8.

Finally, we also applied a random effects analysis to ascertain that the findings of the fixed effects analysis were not driven by a small number of subjects within our group of synesthetes but can be considered representative for the population of grapheme-color synesthetes. Due to the small number of subjects (n = 9), an uncorrected height threshold of $P < 0.001$ and an extent threshold of 20 voxels were applied for this random effects analysis.

Localization of activations

Standard stereotactic coordinates of voxels showing local maximum activation were determined within areas of significant relative changes in neural activity associated with the demands of the different experimental conditions. These local maxima were anatomically localized by reference to a standard stereotactic atlas (Talairach and Tournoux, 1988). For validation of this method of localization, $SPM_{\{Z\}}$ statistics were superimposed on the group mean 3D MR image which was calculated following stereotactic transformation of each individual's 3D MR image into the same standard stereotactic space of the MNI average brain (Friston et al., 1995a) employed as a template by SPM99 (see above).

Results

Behavioral data

The reaction time data recorded during fMRI scanning revealed that the grapheme-color synesthetes took significantly longer to decide whether they experienced synesthesia or not for synesthesia inducing letters (925 ms ± 38 ms) compared to non-inducers (797 ms ± 38 ms, $P < 0.05$). This main effect was influenced by a differential, albeit insignificant, effect of color for synesthesia-inducing letters (+54 ms; C + S+ 952 ms, C − S+ 898 ms) compared to those letters which did not induce synesthesia (+23 ms; C + S− 808 ms, C − S− 785 ms). This (insignificant) interaction suggests that synesthetes experience synesthesia more slowly for colored (952 ms) compared to non-colored letters (898 ms). This might be a behavioral equivalent to prolonged reaction times observed in other studies of synesthesia where 'Stroop'-like effects were elicited when subjects named the surface color of a synesthesia-inducing stimulus. There was a non-significant increase in reaction times for colored (880 ms ± 41 ms) vs. non-colored (842 ms ± 41 ms) letters independent of synesthesia.

Imaging data

The *fixed effects analysis* revealed increased neural activity ($P_{svc} < 0.05$, corrected for region of interest, ROI) associated with physically evoked color perception (i.e., [C + S+ and C + S−] > [C − S+ and C − S−]) in the fusiform gyrus bilaterally (see Table 1A for details). The inverse contrast (i.e., [C − S+ and C − S−] > [C + S+ and C + S−]) did not reveal any significant activation.

In contrast, the experience of synesthesia led to increased neural activity ($P_c < 0.05$, corrected for multiple comparisons) in the left intraparietal cortex only (see Fig. 1 and Table 1B). Interestingly, there were two separate clusters of activation within the left IPS: one was located more anteriorly (corresponding to anterior intraparietal area, AIP) while the other was located more posteriorly (corresponding to caudal intraparietal area, CIP). The inverse contrast did not show any significant activation. Since we had mapped the neural mechanisms underlying color processing per se in our group of synesthetes, we also performed an ROI analysis to disclose activation of the fusiform gyrus in synesthesia. For this analysis we used the simple effect of synesthesia in the absence of surface color (C − S+ > C − S−), since this contrast is the 'purest' one with regard to this specific question. The ROI analysis (10 mm sphere centered upon the activation foci found for the main effect of surface color in our study) revealed a trend for an activation in the left fusiform gyrus only (−32/−45/−13, $t_{max} = 2.8$, $P_{svc} = 0.073$). This result is compatible with previous reports of a subthreshold (Paulesu et al., 1995) or significant (Nunn et al., 2002) activation of the left fusiform gyrus during synesthesia induced by words auditorily presented.

Since the main effect of synesthesia [(C + S+ and C − S+) > (C + S− and C − S−)] could at least in principle be confounded by the mismatch of surface and synesthetic color, which is only present in the condition C + S+, we also analyzed the simple effect of synesthesia in the absence of stimulus color, i.e., C − S+ > C − S−. This analysis confirmed the significant activation of left intraparietal cortex (AIP and CIP; $P_c < 0.05$, corrected for multiple comparisons) and showed an additional significant activation of left premotor cortex (see Table 1D).

Analysis of the interaction term ([C + S+ > C − S+] > [C + S− > C − S−]) revealed a significant interaction ($P_c < 0.05$) in the left dorsolateral prefrontal cortex only (DLPFC, see Table 1C). The second interaction did not reveal any significant neural

Table 1
Fixed effects analysis: relative increases in brain activity during physically evoked and synesthetically perceived color experience as well as during the conflict between the two different color experiences

Region	Side	*x*	*y*	*z*	*t* value
A. Main effect of physically evoked color experience (C + S+ and C + S−) > (C − S+ and C − S−)					
Fusiform gyrus	R	+34	−67	−15	4.3[a]
	L	−32	−53	−17	3.6[a]
B. Main effect of synesthetically perceived color experience (C + S+ and C − S+) > (C + S− and + C − S−)					
Caudal intraparietal cortex	L	−24	−65	+51	5.4**
Anterior intraparietal cortex	L	−36	−50	+41	4.8**
C. Interaction: conflict between physically evoked and synesthetically perceived color experiences (C + S+ > C − S+) > (C + S− > C − S−)					
Dorsolateral prefrontal cortex	L	−42	+15	+25	4.6**
D. Simple effect of synesthetic color experience for non-colored stimuli (C − S+ > C − S−)					
Caudal intraparietal cortex	L	−24	−65	+51	4.5**
Anterior intraparietal cortex	L	−36	−46	+43	4.8**
Premotor cortex	L	−46	+3	+27	5.0**
E. Simple effect of physically evoked color experience in the presence of synesthesia (C + S+ > C − S+)					
Fusiform gyrus	R	+34	−67	−15	4.0*
Dorsolateral prefrontal cortex	L	−42	+15	+25	4.0*

Brain regions showing relative increases of BOLD response associated with each comparison of interest. For each region of activation, the coordinates in standard stereotactic space (Talairach and Tournoux, 1988) are given referring to the maximally activated focus within an area of activation as indicated by the highest *t* value. *x*, distance (mm) to right (+) or left (−) of the midsagittal plane; *y*, distance anterior (+) or posterior (−) to vertical plane through the anterior commissure; *z*, distance above (+) or below (−) the inter-commissural (AC–PC) plane.

C + S+ = colored letters inducing synesthesia; C − S+ = non-colored letters inducing synesthesia; C + S− = colored letters, not inducing synesthesia; C − S− = non-colored letters, not inducing synesthesia.

[a] $P_{svc} < 0.05$ (small volume corrected for region of interest, ROI).

* $P < 0.001$ (uncorrected).

** $P_c < 0.05$ (corrected for multiple comparisons within the whole brain volume).

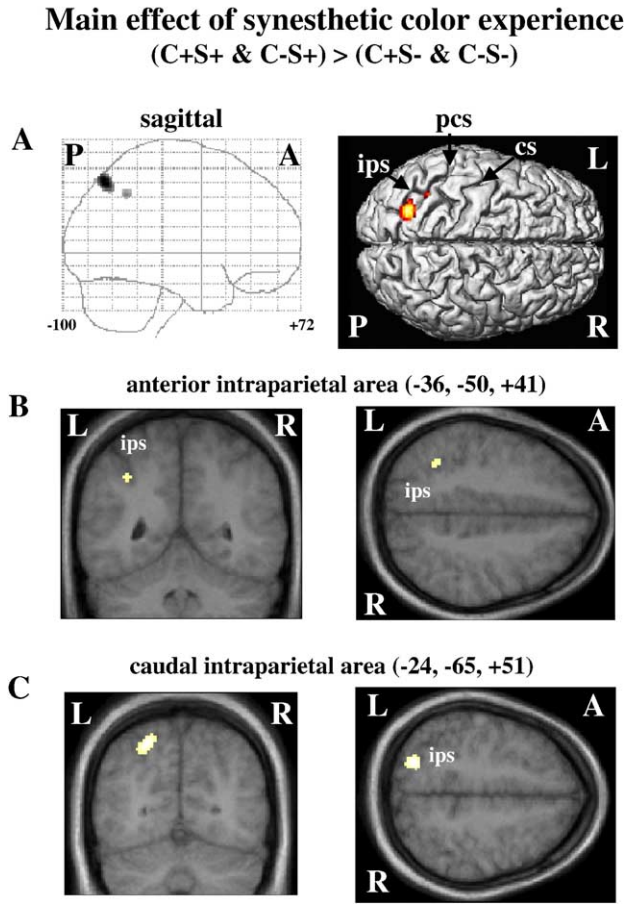

Fig. 1. Relative increases in neural activity ($P_c < 0.05$) associated with synesthesia are found in the left intraparietal cortex with two separate activation foci within the intraparietal sulcus (ips). (A) Left: $SPM_{\{Z\}}$ map, right: projection of the anterior and caudal intraparietal activations onto a 3D surface rendering of a spatially normalized single subject brain. $SPM_{\{Z\}}$ maps of the anterior (B) and caudal (C) intraparietal areas mediating the synesthetic color experience superimposed upon a coronal (left) and an axial (right) section of the group mean magnetic resonance image, spatially normalized into the same stereotactic space (Talairach and Tournoux, 1988). ips = intraparietal sulcus, pcs = postcentral sulcus, cs = central sulcus.

activation. Analysis of the parameter estimates of the maximally activated voxel within the DLPFC (see Fig. 2F) showed that this interaction was due to the extra effect of surface color on synesthetic experience. To show that the interaction term was mainly driven by the simple effect of stimulus color in the presence of synesthesia (C + S+ > C − S+), this simple effect was computed. This additional analysis confirmed the already described significant activation of left DLPFC and additionally revealed a significant activation of the right fusiform gyrus (see Table 1E).

The *random effects analysis* confirmed the results of the fixed effects analysis: the main effect of external color activated the fusiform gyrus bilaterally and the left DLPFC was activated by the interaction term ($P < 0.001$, uncorrected; see Table 2). For the main effect of synesthesia, the two activation foci in the intraparietal cortex were validated. In addition, activations of the left premotor cortex and the right frontal cortex were observed ($P < 0.001$, uncorrected; see Table 2B).

Discussion

There are three main findings in our study: (i) when processing externally presented color, synesthetes activate the color center within the fusiform gyrus bilaterally; (ii) grapheme-color synesthesia activates two areas within the left IPS, which most likely correspond to human AIP and CIP; and (iii) the perceptual mismatch between physically evoked and synesthetic color experiences results in increased neural activity in the left DLPFC.

The factorial design employed allowed us to examine the neural mechanisms associated with processing surface color while controlling for synesthetic color experience (and vise versa): comparing colored with non-colored stimuli revealed increased neural activity in the fusiform gyrus bilaterally. Taking into account the variability of the human color areas, the observed activations (right: +34/−67/−15; left: −32/−53/−17) lie within the V4 complex consisting of V4 proper (left: −26/−68/−8, right: +20/−66/−4) (Bartels and Zeki, 2000) or V8 (±33/−65/−14) (Hadjikhani et al., 1998) and V4α (left: −27/−56/−5; right: +24/−58/−7) (Bartels and Zeki, 2000). In addition, the coordinates of the current study correspond well to the coordinates derived from a group of color-word synesthetes when processing chromatic vs. achromatic Mondrians (right side only: +40/−52/−13) (Nunn et al., 2002). Thus, our and previous functional imaging data suggest that grapheme-color synesthetes process surface color in the same cortical areas as non-synesthetes. Converging psychological evidence for this notion is provided by the normal performance of the grapheme-color synesthetes during our behavioral testing including tests of color vision.

When controlling for neural responses to surface color, grapheme-color synesthesia significantly enhanced neural activity in the left intraparietal cortex with two local maxima, one located in the anterior (most likely corresponding to area AIP; Grefkes et al., 2002) and the other located in the posterior aspect (most likely corresponding to area CIP; Shikata et al., 2003) of the IPS. Activations confined to the left hemisphere most probably reflect the fact that letter processing (8 of the subjects were right-handers, 1 subject was ambidextrous) is a left hemisphere function (Frost et al., 1999; Stephan et al., 2003). Among the different polymodal intraparietal areas, AIP and CIP are known to be concerned with polymodal form processing (Grefkes et al., 2002; Shikata et al., 2003). Importantly, due to the factorial design activation of left intraparietal cortex in our experiment cannot be attributed to differential covert naming (sub-vocalizing) of surface or synesthetic color (Binder et al., 1997). Also, naming is known to involve left frontal and temporal cortices (Perani et al., 1999) rather than the IPS. Previous functional imaging studies of synesthesia also found activation of parietal cortex: bilaterally in the superior parietal lobe (+26/−64/+40 and −30/−62/+40) (Paulesu et al., 1995) and in the left angular gyrus (−40/−58/+35) (Nunn et al., 2002). However, a closer inspection of the figures of two other imaging studies (Aleman et al., 2001; Elias et al., 2003) also reveals neural activity within the IPS. It is conceivable that the significance of these findings was overlooked because of many other areas activated in these imaging studies.

When employing a random effects model (to ensure that the activations in the IPS were not driven by a small subset of the synesthetes) but using an uncorrected threshold (given the overall small sample of synesthetes studied) additional activations were observed. Though we are reluctant to discuss these in great detail we suggest that their activation is consistent with the hypothesis of

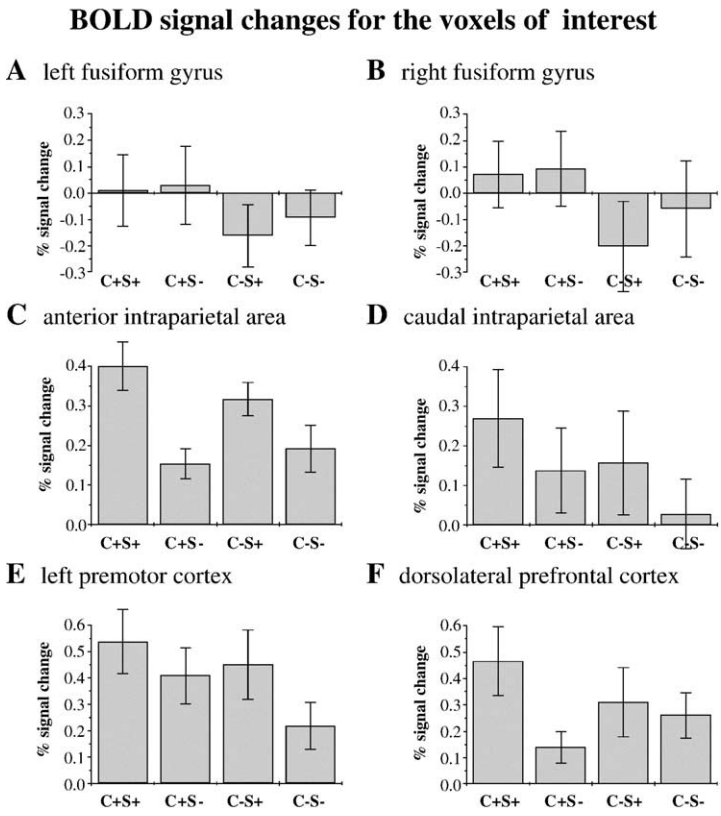

Fig. 2. Plots of relative BOLD signal change for the relevant local maxima in the areas of significantly increased neural activity as a function of the respective experimental conditions. (A and B) Activation of the fusiform gyrus bilaterally by the main effect of color; (C and D) activation of the left anterior (AIP) and caudal (CIP) intraparietal areas by the main effect of synesthesia; (E) activation of the left premotor cortex by the simple effect of synesthetic color experience for non-colored stimuli; and (F) activation of left dorsolateral prefrontal cortex (DLPFC) by the interaction term. The exact coordinates of the local maxima within the areas of activation and their *t* statistics are shown in Table 1. Error bars indicate the SEM. C + S+ = colored letters inducing synesthesia; C − S+ = non-colored letters inducing synesthesia; C + S− = colored letters, not inducing synesthesia; C − S− = non-colored letters, not inducing synesthesia.

cross-modal processing as a key process underlying synesthesia. Left premotor cortex is also part of the network of polymodal areas and heavily connected to the polymodal areas in the intraparietal cortex (Bremmer et al., 2001; Graziano, 2001; see also Rizzolatti and Luppino, 2001 for the intense connection between ventral premotor cortex and AIP).

Our factorial design enabled us to isolate increases in neural activity in intraparietal (and possibly also premotor) polymodal areas in synesthesia over and above any involvement of these areas in letter or color processing per se. We accordingly propose that the observed activations of these polymodal intraparietal (and premotor) areas may reflect a core process underlying synesthesia in the following sense: activation of polymodal neurons in areas AIP and CIP (possibly in concert with neurons in the connected premotor cortex) may constitute a key neural mechanism for the 'binding of alphanumeric form and synesthetic color' previously postulated on the basis of behavioral data (Mattingley et al., 2001; Palmeri et al., 2002). This notion is supported by a PET study showing parietal cortex activation during the perception of forms defined by color cues

Table 2
Random effects analysis: Relative increases in brain activity during physically evoked and synesthetically perceived color experience as well as during the conflict between the two different color experiences

Region	Side	*x*	*y*	*z*	*t* value
A. Main effect of physically evoked color experience (C + S+ and C + S−) > (C − S+ and C − S−)					
Fusiform gyrus	R	+18	−61	−12	5.9*
	L	−20	−53	−12	8.5*
B. Main effect of synesthetically perceived color experience (C + S+ and C − S+) > (C + S− and + C − S−)					
Caudal intraparietal cortex	L	−32	−66	+35	10.5*
Anterior intraparietal cortex	L	−38	−51	+36	5.8*
Middle frontal gyrus	R	+36	+39	−4	10.6*
Premotor cortex	L	−36	+4	+31	7.1*
C. Conflict between physically evoked and synesthetically perceived color experiences (C + S+ > C − S+) > (C + S− > C − S−)					
Dorsolateral prefrontal cortex	L	−42	+20	+25	17.1**

For details see Table 1.

(Gulyas et al., 1994). We suggest that the polymodal intraparietal form areas AIP and CIP fulfill two important prerequisites for a physiological basis of grapheme-color synesthesia: (i) they both represent areas where cross-modal processing may take place (Grefkes et al., 2002); and (ii) they both constitute central areas of visual processing where 'binding' of color and form may occur (Shikata et al., 2003).

Importantly, there was no significant activation of the posterior inferior temporal cortex, another polymodal candidate region for 'binding' color and form in grapheme-color synesthesia. Furthermore, there was only subthreshold activation of the left fusiform gyrus during synesthetic color experiences in the absence of physically evoked color perception. This subthreshold activation of the left fusiform gyrus could also result from top-down modulation (Stephan et al., 2003) of this area by left polymodal intraparietal areas (see also Macaluso et al., 2000).

Based on psychophysical studies, Ramachandran and Hubbard hypothesized that there might be 'higher' and 'lower' grapheme-color synesthetes (Ramachandran and Hubbard, 2001): 'Neural hyperconnectivity' between color and form areas may be present in both groups, but it may occur at different stages of processing. For 'lower' synesthetes, 'hyperconnectivity' may occur already between the color center and the visual grapheme area, i.e., within the fusiform gyrus (Price and Devlin, 2003). In contrast, for 'higher' synesthetes, color-form hyperconnectivity may take place at a higher level of visual processing where cross-modal associations are formed. In addition, Myles et al. (2003) suggest that 'higher' processing of the (stimulus) form occurs before it is associated with synesthetic color, since an identical form, e.g., the ambiguous form Z, could induce different synesthetic colors when it was interpreted as '2' or as 'Z'. Our data specify the polymodal intraparietal (and possibly premotor) areas as the locus of 'hyperconnectivity' in 'higher' grapheme-color synesthetes. This finding is also in good accordance with current theories on normal and abnormal perceptual binding (Robertson, 2003; Sagiv and Robertson, 2005).

Since the main effect of synesthesia in our study may have been influenced (albeit in an insignificant way, since analysis of the interaction did not reveal any effect in the areas showing a main effect) by the mismatch between surface and synesthetic color, which is only present in the condition C + S+, we also analyzed the simple effect of synesthetic experience in the absence of stimulus color, i.e., C − S+ > C − S−. This contrast confirmed the activation of the left polymodal intraparietal (and premotor) areas (see Table 1D). Therefore, although the mismatch between surface and synesthetic color may influence the experience of synesthesia (in fact, all three polymodal areas were strongly activated in the mismatch condition C + S+, see Fig. 2), we suggest that our data support the hypothesis that the activity of polymodal areas constitute a key neural mechanism for the binding of form and synesthetic color independent of the perceptual mismatch.

Finally, grapheme-color synesthetes may experience a feeling of discomfort, when presented with alphanumerical forms, where the surface color does not match the specific synesthetic color triggered: 'The matter [synesthesia] came up, one day in my seventh year, as I was using a heap of old alphabet blocks to build a tower. I casually remarked to her [my mother] that their colors were all wrong' (Nabokov, 1964). This phenomenon can even result in a Stroop-like effect when grapheme-color synesthetes are asked to name the color of a letter which does not match their induced synesthetic color (Mattingley et al., 2001). Although (to avoid movement artefacts) the synesthetes in our fMRI-experiment did not have to name the color of the stimuli, stimulus color influenced – albeit insignificantly – the reaction times of the synesthetes reflecting the mismatch between surface and synesthetic color: the reaction time increase for colored vs. non-colored stimuli was more pronounced for synesthesia-inducing letters than for non-inducing letters. As assessed by the interaction term, this subjective experience of incongruent and hence conflicting color percepts was associated with increased neural activity of left DLPFC. Visual presentation of abnormally colored objects (e.g., a violet banana) also elicits DLPFC activity in non-synesthetes (Zeki and Marini, 1998). While the ACC has been implicated in performance monitoring (Kerns et al., 2004) and response selection (Stephan et al., 2003) during Stroop tasks, the DLPFC is concerned with the implementation of cognitive control during the preparatory phase (MacDonald et al., 2000). Since our synesthetes did not need to name the stimulus color, there was no direct conflict between stimulus properties and responses, which would have activated ACC. However, the mismatch between physically evoked and synesthetic color experience required an increased amount of supervisory cognitive control (Koechlin et al., 2003) during the preparation of the response (see also Milham et al., 2003). Accordingly, the coordinates of the activation within the left DLPFC (−42/+15/+25) in our study closely resemble those of MacDonald et al. (−41/+18/+28) for cognitive control during preparation (MacDonald et al., 2000). In addition, DLPFC has previously been associated with situations in which a 'conflict of the senses' occurs (Fink et al., 1999). One of the cognitive control aspects realized by the DLPFC during that study was bringing to awareness and overcoming any incongruence between different sensory experiences. Similarly, in our study the (grapheme-color) synesthetes experienced incongruent colors. Furthermore, a recent study of non-synesthetes implicates DLPFC in the neural mechanisms that minimize cross-modal distraction (Weissmann et al., 2004). These authors found a close-by activation within left DLPFC (−47, +17, +28) which was related to increased attention to the relevant stimulus letter when conflicting stimuli were present. Similarly, during the mismatch condition the grapheme-color synesthetes in our study had to pay attention to their synesthetic color and avoid being distracted by the surface color of the letter stimuli. Activation of DLPFC also supports the recently proposed architecture of cognitive control in the DLPFC with the caudal part of DLPFC being involved in the evaluation of a stimulus in respect to contextual information (Koechlin et al., 2003). Our data thus imply DLPFC as a key locus for integrating and overcoming conflicting perceptual information in synesthesia by increased cognitive control. The similar neural substrate of cognitive control during this 'conflict of the senses', i.e., activation of the DLPFC in non-synesthetes (Fink et al., 1999; Zeki and Marini, 1998) and synesthetes, provides further support for the perceptual reality of synesthetic experiences.

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